Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults (Review)

Petsky HL, Kynaston JA, Turner C, Li A, Cates CJ, Lasserson TJ, Chang AB

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[Intervention Review]

Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

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ABSTRACT

Background

Asthma severity and control can be measured both subjectively and objectively. Sputum analysis for evaluation of percentage of sputum eosinophilia directly measures airway inflammation, and is one method of objectively monitoring asthma. Interventions for asthma therapies have been traditionally based on symptoms and spirometry.

Objectives

To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults.

Search methods

We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles. The last search was conducted in November 2008.

Selection criteria

All randomised controlled comparisons of adjustment of asthma therapy based on sputum eosinophils compared to traditional methods (primarily clinical symptoms and spirometry/peak flow).

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. Three sets of reviewers selected relevant studies. Two review authors independently assessed trial quality extracted data. Authors were contacted for further information but none were received. Data were analysed as "treatment received" and sensitivity analyses performed.

Main results

Three adult studies were included; these studies were clinically and methodologically heterogenous (use of medications, cut off for percentage of sputum eosinophils and definition of asthma exacerbation). There were no eligible paediatric studies. Of 246 participants randomised, 221 completed the trials. In the meta-analysis, a significant reduction in number of participants who had one or more asthma exacerbations occurred when treatment was based on sputum eosinophils in comparison to clinical symptoms; pooled odds ratio (OR) was 0.49 (95% CI 0.28 to 0.87); number needed to treat to benefit (NNTB) was 6 (95% CI 4 to 32).

There were also differences between groups in the rate of exacerbation (any exacerbation per year) and severity of exacerbations defined by requirement for use of oral corticosteroids but the reduction in hospitalisations was not statistically significant. Data for clinical symptoms, quality of life and spirometry were not significantly different between groups. The mean dose of inhaled corticosteroids per day was similar in both groups and no adverse events were reported. However sputum induction was not always possible.

Authors' conclusions

Tailored asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations in adults with asthma. This review supports the use of sputum eosinophils to tailor asthma therapy for adults with frequent exacerbations and severe asthma. Further studies need to be undertaken to strengthen these results and no conclusion can be drawn for children with asthma.

PLAIN LANGUAGE SUMMARY

Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults

Pharmacological treatment of asthma is tailored based on various subjective or objective outcome measures. The objective of this review was to evaluate the efficacy of tailoring asthma interventions based on sputum eosinophils in comparison to clinical symptoms for asthma related health outcomes in children and adults. Three trials involving 246 adults fulfilled the predetermined criteria but there were no studies in children. Tailored asthma interventions based on sputum eosinophils is beneficial in reducing the frequency and severity of asthma exacerbations in adults with asthma. This review supports the use of sputum eosinophils to tailor asthma therapy only for adults in reducing the frequency and severity of asthma exacerbations. However, as data for clinical symptoms, quality of life and spirometry were not different between the groups, use of sputum eosinophilia cannot be advocated in all settings until more studies are available. As there were no studies in children, no recommendation can be made for children with asthma.

BACKGROUND

The severity and control of asthma in both children and adults can be based on subjective or objective measures. Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality of life questionnaires. Traditional objective measures include peak flow monitoring, spirometry and degree of airway hyper-responsiveness (AHR) (Zacharasiewicz 2005). More recently, markers of airway inflammation (such as sputum eosinophils, exhaled nitric oxide and breath condensate markers) have been advocated for asthma monitoring. These may be more sensitive markers than subjective measures, as they directly measure airway inflammation, in comparison to traditional objective measures (Zacharasiewicz 2005).

Analysis of induced sputum provides similar (but not identical) data to secretions obtained through bronchial wash and bronchoalveolar lavage. Analysis of induced sputum is a reproducible method to study airway inflammation in asthma (Bacci 2002). Sputum analysis is increasingly used as a noninvasive test to determine airway inflammation and may provide useful information in the diagnosis and management of asthma. The markers obtained from induced sputum include cell differential (particularly eosinophils and neutrophils) and eosinophil cationic protein. In asthmatic patients, the percentage of eosinophils in induced sputum is significantly higher than that in non-asthmatic patients (Ohnishi 1998). Neutrophilic airway inflammation has however also been described in people with asthma (Green 2002a).

Assessing airway inflammation by quantitative measurements instead of subjective data potentially allows the physician to tai-

lor personal asthma interventions. However, induced sputum and sputum analysis is labour intensive and not widely available in non-research laboratories. Hypertonic saline, used to induce sputum may also temporarily increase asthma symptoms. A systematic review evaluating the efficacy of tailoring asthma interventions based on sputum analysis (sputum strategy, SS) in comparison with the traditional reliance primarily on clinical symptoms of asthma (CS) will be useful to guide clinical practice.

OBJECTIVES

To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing adjustment of asthma medications based on sputum analysis in comparison to traditional methods (primarily clinical symptoms with or without spirometry/peak flow).

Types of participants

Children and adults with classical asthma. Exclusion criteria: eosinophilic bronchitis, asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive airway disease.

Types of interventions

All randomised controlled trials of adjustment of asthma therapy based on sputum eosinophils in comparison to clinical symptoms/spirometry. Trials that included the use of other interventions will be included if all participants had equal access to such interventions.

Types of outcome measures

Attempts were made to obtain data on at least one of the following outcome measures.

Primary outcome

a) Proportion of participants who had asthma exacerbations during follow up

Secondary outcomes

b) Mean difference in asthma related outcome measures
c) Proportions experiencing adverse effects of the interventions
d) Proportions experiencing complications, for example, requirement for medication change, etc.
The proportions of participants who failed to improve on treatment and the mean clinical improvement were determined using the following hierarchy of assessment measures (i.e. where two or more assessment measures are reported in the same study, the outcome measure that is listed first in the hierarchy was used).
i) Hospitalisation, acute presentations to an emergency facility for asthma, frequency of exacerbations and rescue courses of oral corticosteroids.
ii) Symptomatic (quality of life, Likert scale, asthma diary, visual analogue scale) - assessed by the patient (adult or child).
iii) Symptomatic (quality of life, Likert scale, asthma diary, visual analogue scale) - assessed by the parents/carers.
iv) Symptomatic (Likert scale, visual analogue scale) - assessed by clinicians.
v) Indices of spirometry, peak flow, airway hyper-responsiveness.
vi) Beta-agonist used.

Search methods for identification of studies

We identified trials from the following sources:

1. Cochrane Airways Group Specialised Register of Trials;
2. Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library Issue 4, 2008;
3. MEDLINE (1966 to 2008). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module;
4. OLDMEDLINE (1950 to 1965). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module;
5. EMBASE (1980 to 2008).Topic search strategy combined with the RCT search filter as outlined in the Airways Group module;
6. List of references in relevant publications; and
7. Written communication with the authors of trials included in the review.

All records in the Airways Group register coded as 'asthma' were searched with the following terms: 'sputum* or "airway inflam*" or mucus or phlegm'. For the full search strategies used in other databases see Appendix 1.

Data collection and analysis

Retrieval of studies

From the title, abstract, or descriptors, we reviewed the literature search independently in triplet (AC reviewed all and two sets of review authors: HP paired with AL; AK paired with CT) to identify potentially relevant trials for full review. We searched bibliographies and texts to identify additional studies. From the full text using specific criteria, the same sets of review authors independently selected trials for inclusion. Agreement was measured using kappa statistics. There was no disagreement although it was planned that disagreement would have been resolved by third party adjudication.

We reviewed trials that satisfied the inclusion criteria and recorded the following information: study setting, year of study, source of funding, patient recruitment details (including number of eligible participants), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, co-interventions, numbers of patients not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. Data was extracted on the outcomes described previously and data from included studies was double entered into Review Manager 5 for meta-analysis. Initial attempts to contact the corresponding authors were not successful, but further information may be available for the next update of this review.

Quality assessment

Two review authors (HP and AC) independently assessed the quality of the studies included in the review.). We assessed four components of quality:

1. Allocation concealment. Trials were scored as: Grade A: Adequate concealment, Grade B: Unclear, Grade C: Clearly inadequate concealment. (Grade A = high quality);
2. Blinding. Trials were scored as: Grade A: Participant and care provider and outcome assessor blinded, Grade B: Outcome assessor blinded, Grade C: Unclear, Grade D: No blinding of outcome assessor (Grade A, B = high quality);
3. Reporting of participants by allocated group. Trials were scored as: Grade A: The progress of all randomised participants in each group described, Grade B: Unclear or no mention of withdrawals or dropouts, Grade C: The progress of all randomised participants in each group clearly not described. (Grade A = high quality); and
4. Follow up. Trials scored as: Grade A: Outcomes measured in > 90% (where withdrawals due to complications and side-effects are categorised as treatment failures), Grade B: Outcomes measured in 80 to 90%, Grade C: Unclear, Grade D: Outcomes measured in < 80%. (Grade A = high quality).

While only the allocation concealment quality assessment was displayed in the meta-analysis figures, all assessments were included in the "Characteristics of included studies' table. Inter-reviewer reliability for the identification of high quality studies for each component was measured by the Kappa statistic.

Each study was assessed using a 1 to 5 scale described by Jadad et al (Jadad 1996) and summarised as follows:

Was the study described as randomised? (1 = yes; 0 = no);

Was the study described as double blind? (1 = yes; 0 = no);

Was there a description of withdrawals and dropouts? (1 = yes; 0 = no);

Was the method of randomisation clearly described and appropriate? (1 = yes; 0 = no); and

Was the method of double blinding well described and appropriate? (1 = yes; 0 = no).

Statistics

For the dichotomous outcome, we calculated variables of each individual study, relative and absolute risk reductions using a modified intention-to-treat analysis when the outcome event is beneficial. If the event is non-beneficial (such as exacerbation), 'treatment received' analysis was utilised. A modified intention-to-treat analysis assumes that participants not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies examined whether pooling of results (meta-analysis) is reasonable. This took into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

We included the results from studies that met the inclusion criteria and reported the outcomes of interest in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed-effect model) were calculated (Cochrane statistical package, Review Manager version 5). For Rate Ratios of common events whereby one participant may have more than one event, generic inverse variance (GIV) was utilised. The Rate Ratios were taken from the published papers and the standard errors were calculated from confidence intervals or P values published in the papers. It was planned that for cross-over studies, mean treatment differences would be calculated from raw data, extracted or imputed and entered as fixed-effect GIV outcome, to provide summary weighted differences and 95% confidence intervals. For cross-over trials, it was planned that only data from the first arm were included in meta-analysis if data was combined with parallel studies (Elbourne 2002). Numbers needed to treat to benefit (NNTB) was calculated from the pooled Odds Ratio (OR) and its 95% confidence interval (CI) applied to a specified baseline risk using an online calculator (Cates 2003). The outcome indices were assumed to be normally distributed continuous variables so the

mean difference in outcomes could be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, we estimated the standardised mean difference. Any heterogeneity between the study results was described and tested to see if it reached statistical significance using a chi-squared test. The 95% CI estimate using a random-effects model was included whenever there are concerns about statistical heterogeneity. Heterogeneity is considered significant when the P value is < 0.10 (Deeks 2005).

In one study (Jayaram 2006) it was unclear whether data was analysed based on those who completed the study (N = 102) or based on numbers where data could be analysed (N = 96). We used the conservative number (N = 96) when appropriate.

Subgroup analysis

We had planned to carry out an a priori sub-group analysis for adults versus children.

It was planned that sensitivity analyses be done to assess the impact of the potentially important factors on the overall outcomes:

a) study quality;
b) study size;
c) variation in the inclusion criteria;
d) differences in the medications used in the intervention and comparison groups;
e) differences in outcome measures;
f) analysis using random-effects model;
g) analysis by "treatment received";
h) analysis by "intention-to-treat"; and
i) analysis by study design-parallel and crossover studies.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

From searches conducted in 2005 and 2006, 2502 potentially relevant citations were retrieved from the Cochrane Aorways Group trials register (2436 from 2005 and 66 from 2006). After assessing the abstracts, 65 papers were obtained for consideration to be included into review. Forty-one papers were not relevant as treatment was not based on sputum eosinophils. Twenty-one studies were further excluded for other reasons: the main reason for non-eligibility based on review criteria was the non-controlled, non-randomised nature of the respective studies (see table 'Characteristics of excluded studies'). We contacted one author from an excluded study to clarify a study mentioned in a review article but the treatment was not based on sputum eosinophils (Wark 2003). Another (Bacci 2005) was an abstract and we contacted the author for further information but have not received a reply. Additional searches in subsequent years (November 2007 and 2008) did not identify any further studies.

Included studies

Three studies were included (see 'Characteristics of included studies' table), one was a multi-centre study (Jayaram 2006) and the other two were uni-centre studies (Green 2002; Chlumsky 2006). All studies (Green 2002; Chlumsky 2006; Jayaram 2006) were in adult patients. There were no studies that included children. Two studies were double blind, parallel groups (Green 2002; Jayaram 2006) whereas one was single blind, parallel (Chlumsky 2006) and all were published in English.

In all studies (Chlumsky 2006; Green 2002; Jayaram 2006) asthma management were based on either clinical strategy/symptoms (control arm) or sputum eosinophil strategy (intervention arm). The control arm in the studies differed slightly; two studies (Chlumsky 2006; Green 2002) used the British Thoracic Society asthma guidelines to base their treatment decisions which included traditional assessments of symptoms, peak expiratory flow and use of beta-2-agonists. The second study (Jayaram 2006) used symptoms and spirometry to guide the clinical strategy group. This included daytime symptoms < 4 days per week, night time symptoms < 1 per week, need for short-acting beta-2-agonists <4 times per week and FEV1 = 80% of the participants personal best. The intervention arm in the studies, although primarily based on sputum eosinophil percentage, also differed slightly. In Green et al's study, anti-inflammatory treatment was based on maintaining sputum eosinophil count below 3% with a minimum dose of anti-inflammatory treatment (Green 2002; Chlumsky 2006). In Jayaram et al's study, medications were adjusted to keep sputum eosinophils to = 2% using inhaled steroids (Jayaram 2006). In Chlumsky et al's study, medications were based on maintain the sputum eosinophil count below 8% (Chlumsky 2006).

The follow up of the three studies also differed: one of the studies (Green 2002) ran for 12 months with the participants being assessed nine times; Jayaram 2006 ran for two years duration with monthly visits for one year or at exacerbation, then three monthly visits or at exacerbations for the second year; and Chlumsky 2006 had a study duration of 18 months with three monthly visits. Jayaram 2006 defined exacerbations as a loss of symptomatic control requiring increased use of short acting beta2-agonists by = 4 extra puffs per day for a minimum of 48 hours, or by nocturnal symptoms, or early morning wakening due to respiratory symptoms two or more times in one week. Severe exacerbations were defined as requiring rescue courses of oral prednisone as defined

by the investigator. Green 2002 defined severe exacerbations as a decrease in morning peak expiratory flow to more than 30% below baseline value on = 2 consecutive days, or deterioration in symptoms needing rescue course of oral corticosteroid. Chlumsky 2006 defined an exacerbation as a doubling of the frequency of symptoms or number of puffs of rescue salbutamol or a reduction in morning PEF by 30% or more on at least two consecutive days or two of the aforementioned or all three.

Adverse events were not reported in either study. We requested further information from the authors to allow data to be entered into RevMan for meta-analysis. None of the authors replied to requests for further information regarding their published data.

Risk of bias in included studies

Two studies (Green 2002; Jayaram 2006) had Jadad scores of 5, whereas (Chlumsky 2006) scored 3. In two studies (Green 2002; Jayaram 2006) blinding, reporting of participants by allocated group and follow up were of high quality. Allocation concealment was clearly described in two studies (Green 2002; Chlumsky 2006) but unclear in the other (Jayaram 2006). Thus one study (Green 2002) scored "high quality" in all four categories and the other two (Chlumsky 2006; Jayaram 2006) score 3 in the high quality scale. The agreement between the two sets of review authors was good (kappa score for Jadad scale was 1.0 and quality assessment scores was 0.61).

Effects of interventions

The three studies (Green 2002; Chlumsky 2006; Jayaram 2006) included 246 randomised participants with 221 completing the trials. However, one study commented that analysis was possible from an additional six participants (Jayaram 2006).

Asthma exacerbations

All papers (Chlumsky 2006; Green 2002; Jayaram 2006) used asthma exacerbations as the primary outcome and all described a significant reduction in various aspects of asthma exacerbations in the arm that utilised treatment based on sputum eosinophils (SS) when compared to the clinical symptom (CS) arm (control arm whereby treatment was based primarily on clinical symptoms). All studies reported a significant difference between groups in exacerbation data with SS group experiencing fewer exacerbations than the CS group. However, some but not all data that relate to exacerbations could be combined for meta-analysis. Also, the definition of exacerbation of the studies differed; Green and colleagues used the presence of a severe exacerbation defined as "a decrease in the morning peak expiratory flow to more than 30% below the baseline value on two or more consecutive days, or deterioration in symptoms needing treatment with oral corticosteroids" and did not report on mild exacerbations (Green 2002). In contrast, Jayaram et al defined exacerbation as "worsening (from control values) of symptoms requiring increased use of SABA by four or more extra puffs/day for a minimum of 48 h, or by nocturnal symptoms, or early morning wakening due to respiratory symptoms two or more times in one week, with or without a reduction in FEV1 of at least 20%" (Jayaram 2006). Chlumsky 2006 defined an exacerbation as a doubling of the frequency of symptoms or number of puffs of rescue salbutamol or a reduction in morning PEF by 30% or more on at least two consecutive days, two of the aforementioned or all three. The patients were instructed to take 16 mg methylprednisolone each morning for 10 days and to call the treating physician if they fulfilled the exacerbation criteria. Outcomes are described below

1. Any exacerbation (Comparison 01)

(a) Number of participants who had one or more exacerbations (as defined by authors) during the study period (Outcome 01)

Meta-analysis from data combined from all studies showed that the number of participants experiencing any exacerbation was significantly less (P = 0.01) in the SS group than the CS group. Pooled OR estimate effect was 0.49 (95% CI 0.28 to 0.87; Analysis 1.1). The NNTB was 6 (95% CI 4 to 32).

(b) Frequency of any exacerbation (per participant-month) (Outcome 02)

Use of the SS significantly reduced frequency of exacerbations compared to CS, rate ratio of 0.54 (95% CI 0.37 to 0.78; Analysis 1.2). There was heterogeneity between the studies (I2 = 55%).

(c) Time to first exacerbation

The three studies reported that SS group had significantly longer time to first exacerbation compared to CS group (Green 2002; Chlumsky 2006; Jayaram 2006). However, the data from the studies could not be combined.

2. Exacerbations classified by severity of exacerbation (Comparison 02)

(a) Hospitalisation (Outcome 01)

None of the participants in Jayaram's or Chlumsky's studies were hospitalised whereas seven in Green's study were hospitalised. Combined data showed no difference between the groups (P = 0.08) but favoured the SS group. OR was 0.14 (95% CI 0.02 to 1.25).

(b) Severe exacerbations requiring rescue oral corticosteroids (Outcome 02)

Severe exacerbations defined by requirement for rescue oral corticosteroids, were significantly less in the SS group compared to the CS group, Rate Ratio of 0.33 (95% CI 0.19 to 0.57), with no significant heterogeneity between the studies (I2 = 0%, P = 1.0).

(c) Mild exacerbations (Outcome 03)

Data on mild exacerbations were only available in one study (Jayaram 2006). As the definition of severe exacerbations (other than that defined in 2a and 2b) differed between the studies, the data was not combined. Comparing occurrence of exacerbation types (mild versus severe), there was a significant difference between groups (Chi2 5.29, df = 1, P = 0.02) suggesting that mild exacerbations were not reduced as much as severe exacerbations.

3. Eosinophilic Exacerbations (Comparison 03)

Jayaram and colleagues reported types of asthma exacerbations in each group (Jayaram 2006). Sputum could only be obtained in 39 of the 47 exacerbations in the SS group and 63 of the 79 total exacerbations in the CS group. Those exacerbations where sputum could be obtained were classified as eosinophilic or non eosinophilic and this indicated that the overall reduction in exacerbation rate was largely due to a reduction in eosinophilic exacerbations in this study.

4. Exacerbations Subgrouped by asthma severity (Comparison 04)

(a) Any exacerbation (Relative Risk) by severity of asthma (Outcome 01)

Green and colleagues did not subgroup participants by asthma severity (Green 2002) nor did Chlumsky 2006. Jayaram and colleagues analysed data based on daily requirement for ICS and LABA. Asthma severity was defined based on minimum daily maintenance fluticasone (mild asthma = requiring < 250 ug/day; moderate to severe asthma = requiring = 250 ug/day) (Jayaram 2006).Those with mild asthma (< 250 ug/day fluticasone equivalent) showed no significant difference in Relative risk of exacerbation (RR 1.34; 95% CI 0.52 to 3.46). Those with moderate to severe asthma (= 250 ug/day fluticasone equivalent) also showed no significant difference between groups in the relative risk (RR) of exacerbation, although the outcome favoured the SS group (RR 0.63, (95% CI 0.38 to 1.03). The difference between these subgroup effects was not significant (Chi2 1.93, df = 1, P = 0.19).

(b) Any exacerbations (Relative Risk), by use of long acting beta2 agonists (LABA) (Outcome 02)

Green and colleagues reported equal numbers of participants in both groups being treated with LABA (N = 12) but outcomes based on those on LABA were not available (Green 2002). Data from Jayaram did not show a significant difference between the effect on exacerbations in those taking LABA (RR 0.53, 95% CI 0.25 to 1.14) or those not on LABA (RR 1.05, 95% CI 0.62 to 1.78), (Chi2 2.07, df = 1, P = 0.15).

5. Secondary outcomes

Green and colleagues reported other outcomes: nitric oxide was 48% lower in SS group in comparison to CS group at the end of study. The improvement in methacholine PC20 was significantly better in the SS group compared to the CS group at 6 months (doubling doses 1.0 versus -0.7, P = 0.03) and 12 months (0.2 versus -1.3, P = 0.015). However, the visual analogue symptom scores, total asthma quality of life scores, peak expiratory flow amplitude (% mean), FEV1 after bronchodilator use and the use of rescue beta-2-agonists did not differ between the two groups in Green and colleagues study (Green 2002). Jayaram and colleagues did not report these outcomes; although asthma quality of life (QoL) assessments were undertaken, these results were not published (Jayaram 2006)]. Chlumsky et al's study also reported no difference between groups for FEV1 change and they did not report on symptoms or QOL (Chlumsky 2006).

6. Mean daily dose of corticosteroid use (Comparison 05)

(a) Inhaled corticosteroid (Outcome 01)

All three studies reported no differences in ICS use between groups. The SD for the groups were not available in Jayaram's paper and was estimated based on the data from Green's paper. Forest plots showed no significant difference between the groups. Pooled WMD 78.99 (95% CI -90.13 to 248.11).

(b) Oral corticosteroids (Outcome 02)

Only Green and colleagues reported on mean oral corticosteroids use and described no difference between the groups (mean difference of -0.40, 95% CI -2.36 to 1.56) (Green 2002). Meta-analysis was not possible.

7. Cost (Comparison 06)

Green and colleagues described estimated cost per patient per year and there was no significant difference between the groups (mean difference of -314, 95% CI -941.27 to 313.27) (Green 2002). Data from the other two studies were not available.

8. Other results

Sputum induction was not always successful; in Green's study, sputum induction was successful in 552 of 632 attempts (87%) (Green 2002) and 102 out of a total of 126 (81%) in Jayaram and colleagues' study (Jayaram 2006). Chlumsky 2006 did not report their success rate in obtaining sputum. No other adverse events were reported in the studies.

Sensitivity Analyses

In the outcome of number of participants with one or more exacerbations during the study period (comparison 01.01), analyses based on 'intention to treat' (ITT) altered pooled OR only slightly from 0.49 (95% CI 0.28 to 0.87) for 'treatment received' to 0.50 (0.28 to 0.88). The NNTB changed from 6 (95% CI 4 to 32) to 7 (95% CI 4 to 35). Re-analysis of the data based on the less conservative numbers (i.e. use of total of 102 as opposed to 96) for Jayaram and colleagues study (Jayaram 2006) did not change the direction or significance of any of the outcomes. Likewise re-analysis of data based on ITT did not alter direction or significance of effects. In the outcomes described above, significant heterogeneity was only found in subgroup comparisons and thus no sensitivity analyses were performed for this. Also, as there were only two studies in this review, re-analyses by study quality, size, etc were not possible.

DISCUSSION

This meta-analysis based on three moderate to high quality studies in 246 adults (221 completed) has shown that tailoring asthma interventions based on a sputum strategy (% eosinophils) in comparison with usual traditional methods (based primarily on clinical symptoms) is effective in reducing the frequency and the severity of exacerbations (defined by requirement for rescue oral corticosteroids). The NNT to reduce number of participants with one or more exacerbations was 6 (95% CI 3 to 31). However, the difference between groups was inconsistently significant for other outcomes although all favoured the group based on sputum analysis. The mean dose of inhaled corticosteroids per day was similar in all groups. In subgroup analysis, significant heterogeneity for exacerbation rate was found between those also on and off LABA (I2 = 69.3%). Significant heterogeneity was also present between rate of eosinophilic versus non eosinophilic exacerbation but there was no heterogeneity for participants with mild asthma versus those with moderate asthma classified according to amount of ICS use per day.

Asthma management based on sputum eosinophilia was effective in reducing the number of participants who had one or more exacerbations during the study period. It was also effective in reducing the number of exacerbations per person and the number of rescue oral corticosteroids required by the SS group. The effects of treatment based on sputum eosinophils compared with clinical symptoms alone are likely to be due to a reduction in eosinophilic exacerbations (comparison 03.01) rather than non-eosinophilic exacerbations. Thus the benefit of using sputum eosinophilia to tailor asthma treatment is arguably limited in settings where neutrophilic exacerbations (areas of with high environmental pollution (Leigh 1999) or viral induced exacerbations (Wark 2002)) are more frequent than eosinophilic exacerbations. Subgroup analysis from Green 2002 reported that patients with non-eosinophilic inflammation had a reduction in daily inhaled corticosteroids at the end of the study in comparison with baseline when using the sputum strategy. In contrast, the BTS management group had an increase in daily inhaled corticosteroids. However, there no overall reduction in overall mean dose of ICS or oral corticosteroids (Outcomes 04.01 and 04.02).

There was no significant heterogeneity between the studies for any of the outcomes of significance although the participants were on different amounts of maintenance dose of ICS at enrolment; Green et al's study: mean of 1680 to 1930 ug/person/day budesonide equivalent (Green 2002); Chlumsky et al's study: mean 1418 to 1695 ug/person/day budesonide equivalent (Chlumsky 2006) and that of Jayaram et al's study was 1000 (Jayaram 2006). Also the percentage of sputum eosinophilia used to guide therapy differed significantly, ranging from 2% cut-off in Jayaram's study to 8% in Chlumsky's study. Furthermore the definition of exacerbation varied between the studies. Thus while statistical heterogeneity was absent, clinical heterogeneity was arguably present.

Theoretically the use of sputum to guide asthma therapy may result in significant differences in doses of oral or ICS. This meta-analysis has shown that there was no significant differences in the amount of corticosteroids (inhaled or oral) used between the two groups. Also, Green 2002 reported that the annual cost was not significantly cheaper in the SS group in comparison to the CS group.

In contrast to the favourable data in the outcome of exacerbations that support the use of sputum to guide asthma therapies in adults, there was a glaring lack of difference between the groups in symptoms of asthma (VAS score, QoL and beta agonist use). While exacerbations are an important outcome, arguably subjective measures of asthma control are also important. Thus, although this meta-analysis that has shown that monitoring airway inflammation through eosinophils in induced sputum is useful in reducing exacerbations, it is arguable that it cannot be universally advocated. Furthermore, sputum analysis is restricted to laboratories with specific expertise in inducing and analysing sputum. Obtaining and analysing sputum is relatively time consuming (when compared to exhaled nitric oxide) and is not always successful. Also, it can be very difficult to obtain satisfactory samples in young children. Nevertheless use of sputum induction to guide asthma therapy is most likely to be beneficial in adults with severe asthma and those

with frequent exacerbations.

Limitations of review

This systematic review is limited to three studies with only 221 participants completing the trials. While the studies shared some common issues, there are also significant differences, notably, the definition of asthma exacerbation and cut off for sputum eosinophilia were different. Green 2002 and Chlumsky 2006 used an objective measurement to define exacerbations (reduction in peak flow) whereas Jayaram 2006 utilised subjective symptoms (morning waking, etc), the cut-off of % sputum eosinophils to alter therapy, and baseline characteristics. Furthermore, Jayaram 2006 failed to report patients' subjective data from the asthma quality of life survey.

AUTHORS' CONCLUSIONS

Implications for practice

The results from this review suggests that tailoring asthma interventions based on sputum eosinophils instead of primarily on clinical symptoms decreases frequency and severity of asthma exacerbations, especially eosinophilic exacerbations. However, as data for clinical symptoms, QOL and spirometry were not different between groups, use of sputum eosinophilia cannot be advocated in all settings until more studies are available. Nevertheless, asthma interventions based on sputum eosinophils is advocated in adult patients with severe or frequent exacerbations. As there is no data on children, no recommendations for or against tailoring asthma medications based on sputum eosinophilia can be made.

Implications for research

Further RCTs with groups stratified by asthma severity and type of airway inflammation (eosinophilic or neutrophilic) are required. The trials need to include children as well as adults. The design of future RCT's should preferably be multi-centre studies and include other objective measures of asthma including exhaled nitric oxide in addition to the sputum analysis and traditional outcomes of spirometry and peak flow. Subjective outcome measures should also be determined including scores for asthma control and quality of life. Analysis of costs and possible adverse events of inhaled and oral corticosteroids would also provide additional important information.

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REFERENCES

References to studies included in this review

Chlumsky 2006 *{published data only}*
Chlumsky J, Striz I, Terl M, Vondracek J. Strategy aimed at reduction of sputum eosinophils decreases exacerbation rate in patients with asthma. *Journal of International Medical Research* 2006;**34**(2):129–39.

Green 2002 *{published data only}*
Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;**360**(9347):1715–21.

Jayaram 2006 *{published data only}*
Jayaram L, Pizzichini MM, Cook RJ, Boulet L-P, Lemiere C, Pizzichini E, et al.Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *European Respiratory Journal* 2006;**27**(3):483–94.

References to studies excluded from this review

Aldridge 2002 *{published data only}*
Aldridge RE, Hancox RJ, Cowant JO, Frampton CM, Town GI, Taylor DR. Eosinophils and eosinophilic cationic protein in induced sputum and blood: effects of budesonide and terbutaline treatment. *Annals of Allergy Asthma Immunology* 2002;**89**(5):492–7.

Foresi 2005 *{published data only}*
Foresi A, Mastropasqua B, Chetta A, D'Ippolito R, Testi R, et al.Step-down compared to fixed-dose treatment with inhaled fluticasone propionate in asthma. *Chest* 2005;**127**(1):117–24.

Gauvreau 2005 *{published data only}*
Gauvreau GM, Watson RM, Postma DS, de Monchy GR, Deschesnes F, Boulet L. Effect of ciclesonide 40 µg and 80 µg on early and late asthmatic reactions, and sputum eosinophils after allergen challenge in patients with mild asthma. Journal of Allergy & Clinical Immunology. 2005; Vol. 115:S210.

Giannini 2000 *{published data only}*
Giannini D, Di Franco A, Cianchetti S, Bacci E, Dente FL,

Vagaggini B, et al.Analysis of induced sputum before and after withdrawal of treatment with inhaled corticosteroids in asthmatic patients. *Clinical & Experimental Allergy* 2000; **30**(12):1777–84.

Gibson 2001 *{published data only}*
Gibson PG, Saltos N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: A randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine* 2001;**163**(1):32–6.

Griese 2000 *{published data only}*
Griese M, Koch M, Latzin P, Beck J. Asthma severity, recommended changes of inhaled therapy and exhaled nitric oxide in children: a prospective, blinded trial. *European Journal of Medical Research* 2000;**5**(8):334–40.

Jatakanon 1997 *{published data only}*
Jatakanon A, Kharitonov SA, Lim S, Chung KF, Barnes PJ. The effect of differing dosages of inhaled budesonide on asthmatic airway inflammation assessed by induced sputum. *European Respiratory Journal* 1997;**10**(Suppl 25):105s.

Jatakanon 1998 *{published data only}*
Jatakanon A, Lim S, Chung KF, Barnes PJ. An inhaled steroid improves markers of airway inflammation in patients with mild asthma. *European Respiratory Journal* 1998;**12**(5): 1084–8.

Leigh 2000 *{published data only}*
Leigh R, Belda J, Parameswaran K, Hussack P, Efthimiadis A, Pizzichini MMM, et al.Symptomatic patients with mild asthma with non-eosinophilic airway inflammation do not benefit from increased inhaled steroid treatment: a randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine* 2000;**161**:A188.

Lonnkvist 2001 *{published data only}*
Lonnkvist K, Hellman C, Lundahl J, Hallden G, Hedlin G. Eosinophil markers in blood, serum, and urine for monitoring the clinical course in childhood asthma: Impact of budesonide treatment and withdrawal. *Journal of Allergy & Clinical Immunology* 2001;**107**(5 Suppl):812–7.

Meijer 2002 *{published data only}*
Meijer RJ, Postma DS, Kauffman HF, Arends LR, Koeter GH, Kerstjens HA. Accuracy of eosinophils and eosinophil cationic protein to predict steroid improvement in asthma. *Clinical & Experimental Allergy* 2002;**32**(7):1096–103.

Nocker 2000 *{published data only}*
Nocker RE, Out TA, Weller FR, de Riemer MJ, Jansen HM, van der Zee JS. Induced sputum and bronchoalveolar lavage as tools for evaluating the effects of inhaled corticosteroids in patients with asthma. *Journal of Laboratory & Clinical Medicine* 2000;**136**(1):39–49.

Prehn 2000 *{published data only}*
Prehn A, Seger RA, Torresani T, Molinari L, Sennhauser FH. Evaluation of a clinical algorithm involving serum eosinophil cationic protein for guiding the anti-inflammatory treatment of bronchial asthma in childhood. *Pediatric Allergy & Immunology* 2000;**11**(2):87–94.

Smith 2005 *{published data only}*
Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *New England Journal of Medicine* 2005;**352**(21):2163–73.

Van Rensen 1999 *{published data only}*
Van Rensen ELJ, Evertse CE, van Schadewijk WAA, Zwinderman AH, Sterk PJ. Comparison of changes in exhaled nitric oxide, sputum eosinophils and histamine hyperresponsiveness in patients with mild asthma treated with inhaled steroids. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(3 Suppl):A608.

Wark 2003 *{published data only}*
Wark AB, Gibson PG. Clinical usefulness of inflammatory markers in asthma. *American Journal of Respiratory Medicine* 2003;**2**(1):11–9.

Wilson 2000 *{published data only}*
Wilson NM, Bridge P, Spanevello A, Silverman M. Induced sputum in children: feasibility, repeatability, and relation of findings to asthma severity. *Thorax* 2000;**55**(9):768–74.

Zacharaisiewicz 2005 *{published data only}*
Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T, et al.Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *American Journal of Respiratory and Criticail Care Medicine* 2005;**171**(10):1077–82.

Zubovic 2003 *{published data only}*
Zubovic I, Rozmanic V, Ahel V, Banac S. Assessment of treatment by measuring the level of eosinophylic cation protein (ECP) in the serum of children with asthma. *Paediatria Croatica* 2003;**47**(3):145–8.

References to studies awaiting assessment

Bacci 2005 *{published data only}*
Bacci E, Di Paco A, Garbella E, Cianchetti S, Tonelli M, Masino E, et al.Treatment step-up strategy based on sputum eosinophil levels does not yield any better results than standard strategy [abstract]. *European Respiratory Journal* 2005;**26**(Suppl 49):3683.

Bush 2005 *{published data only}*
Bush A. The use of inflammatory markers to guide therapy in children with severe asthma [abstract]. www.clinicaltrials.gov/ct/show/NCT00262340 2005.

Shimonda 2006 *{published data only}*
Shimonda TT, Kishikawa RR, Shoji SS, Nishima SS. Efficacy of airway anti-inflammatory treatments evaluated with airway inflammation markers in patients with cough variant asthma budesonide versus montelukast [abstract]. *Journal of Allergy and Clinical Immunology* 2006;**117**(2 Suppl 1):S176.

Sosa 2004 *{published data only}*
Sosa IP, Nanulescu M. Induced sputum--means for detecting bronchial inflammation in children with atopic bronchial asthma and treatment monitoring [Sputa indusa—-metoda

de evidentiere a inflamatiei bronsice la copiii cu astm bronsic atopic si de monitorizare a tratamentului]. *Pneumologia* 2004;**53**(3):79–84.

Additional references

Bacci 2002

Bacci E, Cianchetti S, Carnevali S, Bartoli ML, Dente FL, Di Franco A, et al.Induced sputum is a reproducible method to assess airway inflammation in asthma. *Mediators of Inflammation* 2002;**11**(5):293–8.

Cates 2003

Cates C. Visual Rx. Online NNT Calculator. http://www.nntonline.net/: Cates C, 2003.

Deeks 2005

Higgins JPT, Green S, editors. Analysing and presenting results. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]*. Chichester, UK: John Wiley & Sons, Ltd., 2005:137.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Green 2002a

Green RH, Brightling CE, Woltmann G, Parker D, Wardlow AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids.. *Thorax* 2002;**57**(10):875–9.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al.Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Leigh 1999

Leigh R, Hargreave FE. Occupational neutrophilic asthma. *Canadian Respiratory Journal* 1999;**6**:194–6.

Ohnishi 1998

Ohnishi H, Maeda H, Nishimura Y, Yokoyama M. Benefits of induced sputum for the evaluation of therapeutic efficacy in patients with bronchial asthma. *Kobe Journal of Medical Sciences* 1998;**44**(4):149–61.

Wark 2002

Wark PA, Johnston SL, Moric I, Simpson JL, Hensley MJ, Gibson PG. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. *European Respiratory Journal* 2002;**19**:68–75.

Zacharasiewicz 2005

Zacharasiewicz A, Wilson N, Lex C, Erin E, Li A, Hansel T, et al.Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *American Journal of Respiratory and Clinical Care Medicine* 2005;**171**(10):1077–82.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chlumsky 2006

Methods	An open, prospective, randomised, parallel-group trial comparing standard strategy of asthma severity assessment (standard strategy) with a strategy based on reducing the number of sputum eosinophils (EOS strategy) over a period of 18 months Patients were stratified by dose of inhaled steroids, treatment with systemic steroids and add-on therapy with inhaled long acting beta-2-agonists and theophyllines Decisions in EOS strategy was made by an independent physician who was blinded to the patients' clinical data and telephoned the subjects within one week after a study visit There were 4 drop outs (all in standard strategy); 2 withdrew for protocol violation and 2 were lost to follow-up The subjects were assessed every 3 months for 18 months.
Participants	55 patients were randomised. Standard strategy N=25, mean age 48 (SD 16), 6 males, 15 females. EOS strategy N=30, mean age 42 (SD 19), 13 males, 17 females. Visiting an outpatients department. Inclusion criteria: FEV1 31-110% predicted, daily dose of inhaled corticosteroid 800-6400ug budesonide or equivalent, diagnosis of asthma confirmed with bronchodilator response greater than 15% after 200ug salbutamol and/or diurnal peak expiratory flow variation of >20% on at least 4 of 14 days run-in period. Exclusion criteria: Current smokers and no upper respiratory tract infections within a month preceding the study
Interventions	The subjects were run-in for 2 weeks and then attended outpatients in the morning at 3 monthly intervals for the 18 months Standard strategy arm: treatment decisions were based on morning PEF variation, frequency of daytime symptoms or short acting beta-2-agonists (SABA) use/week, frequency of night time symptoms or SABA/ week. EOS strategy: treatment decisions were based on the same as the standard strategy arm plus sputum eosinophils % of total cell count
Outcomes	Primary outcome: rate of asthma exacerbations. Secondary outcomes: FEV1, post bronchodilator FEv1 and FEV1/inspiratory vital capacity ratio
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane grade A)

Green 2002

Methods	Randomised, double blind, parallel study comparing asthma management based on British Thoracic Society (BTS group) asthma guidelines or by normalising sputum eosinophil count (Sputum management group). Patients were stratified by number of oral corticosteroids used in the previous 12 months, the baseline induced sputum eosinophil count and baseline methacholine PC20 Neither the physicians nor the subjects were aware of which group they were randomised to or the treatment protocol. At completion of the study each participant was asked to guess which group they were in There was 14 drop outs, 8 during run in and 6 during follow-up The study ran for 12 months and the subjects were assessed 9 times
Participants	74 adults randomised from 82 recruited subjects. Sputum management group n=37: median age 50, range 19-73, 19 males, 18 females. BTS management group n=37: median age 47, range 20-75, 21 males, 16 females. Attending one of 3 specialists clinics at Glenfield Hospital, Leicester, UK Inclusion: diagnosis of asthma and needed hospital follow-up. Exclusion: current smokers, had a history of smoking more than 15 packs/year, clinical important co-morbidity, poor compliance, inadequately controlled aggravating factors e.g. rhinitis or GOR, had severe asthma exacerbation within 4 weeks of entry
Interventions	Outpatient visits were at baseline, month 1, 2, 3, 4, 6, 8, 10, 12. BTS management group: treatment decisions were based on traditional assessments of symptoms, peak expiratory flow and use of beta-2-agonists. Sputum management group: anti-inflammatory treatment was based on maintenance of sputum eosinophil count below 3% with a minimum dose of anti-inflammatory treatment
Outcomes	1. Number of severe asthma exacerbations 2. Control of eosinophilic airway inflammation measured by the induced sputum eosinophil count 3. Exhaled nitric oxide concentrations 4. Symptom scores (0 to 3 for daytime and nighttime symptoms) 5. Total asthma quality-of-life scores 6. Peak flow amplitude as a proportion of the mean 7. FEV1 8. Changes from baseline of methacholine PC20 9. Drug use 10. Admissions for asthma
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane grade A)

Jayaram 2006

Methods	Randomised, double blind, parallel group, effectiveness study. It was a multicentre study over a 2 year period. Stratified by duration of the asthmatic symptoms (<=20 years or >20 years), inhaled corticosteroid dose (equivalent to fluticasone <=500 or >500ug/day) and FEV1 (<=70% or >70% predicted) Subjects blinded to sputum cell counts. Physicians blinded to sputum cell count in clinical strategy group Drop outs: 15 drop outs including 5 who were excluded due to protocol violations by investigator
Participants	117 randomised out of 140 approached. Clinical strategy group n=52;mean age 43.5 (SD 13.9), 15 males, 37 females. Sputum strategy group n=50; mean age 46 (SD 13.8), 15 males, 35 females. Attending one of 3 Canadian or 1 Brazilian chest clinic. Inclusion criteria: symptoms of asthma for a minimum of a year. Exclusion criteria: not mentioned.
Interventions	Clinical strategy: guided by symptoms and strategy Sputum strategy: dose of inhaled steroid was guided solely by induced sputum eosinophils to keep <2%. Spirometry and symptoms were used to identify clinical control, exacerbations and other treatment
Outcomes	1. Relative risk reduction for the first exacerbation 2. The length of time without exacerbations 3. Type and severity of exacerbations 4. The usefulness of monitoring sputum cell counts in relation to the overall severity of asthma. Defined by the minimum dose of inhaled steroid to maintain control 5. The cumulative dose of inhaled steroid needed in Phase 2 adjusted for its duration
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

BTS: British Thoracic Society; FEV1: Forced expiratory volume in 1 second; N: number; PEF: Peak expiratory flow; SABA: Shory-acting beta-agonist; SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aldridge 2002	Randomised, placebo-controlled, crossover study of terbutaline and budesonide, comparing the changes in eosinophil counts and ECP in induced sputum and blood. Excluded as treatment was not adjusted according sputum eosinophil counts

(*Continued*)

Foresi 2005	Randomised, double-blind, parallel study treating one group with fluticasone propionate 1000ug/day and then reducing to 200ug/day in comparison to a fixed dose of fluticasone 200ug/day in the control of bronchial hyperresponsiveness to methacholine and eosinophilic inflammation. Excluded as treatment was not adjusted using sputum eosinophils
Gauvreau 2005	Excluded as treatment was not adjusted according to sputum eosinophils. Randomised, double blind, crossover study of ciclesonide versus placebo after allergan challenge
Giannini 2000	Excluded as treatment not adjusted according to sputum eosinophil counts. Randomised, double blind, placebo controlled study of beclomethasone dipropionate versus placebo
Gibson 2001	Randomised, double blind, placebo controlled, crossover trial of single dose of budesonide 2400ug versus placebo and effect on sputum eosinophils and mast cells in adults with asthma. Excluded as treatment was not based on sputum eosinophil count
Griese 2000	Non RCT nor treatment based on sputum eosinophil count. Prospective study to assess exhaled nitric oxide in comparison to clinical symptoms, treatment adjusted using clinical symptoms
Jatakanon 1997	Randomised, double blind, crossover study of budesonide versus placebo. Excluded as treatment not based on eosinophil count
Jatakanon 1998	Excluded as treatment not based on sputum eosinophils. Randomised into two double blind, placebo controlled studies (1 was parallel study involving 3 groups receiving either budesonide 100ug/day, budesonide 400ug/day or placebo the second was a crossover randomised to receive budesonide 1600ug or placebo
Leigh 2000	Excluded as treatment not adjusted based on sputum eosinophils. RCT of budesonide versus placebo in patients with mild to moderate asthma who had non-eosinophilic airway inflammation
Lonnkvist 2001	Treatment not adjusted according to sputum eosinophil. RCT of budesonide versus placebo in children with mild to moderate asthma. Investigated the effect of withdrawing inhaled budesonide on eosinophil count in blood and eosinophil proteins in serum and urine, and the relationship between these markers and symptoms of asthma
Meijer 2002	Excluded as treatment not adjusted according to sputum eosinophils. Randomised to either prednisolone 30mg/day, fluticasone propionate 2000ug/day or fluticasone propionate 500ug/day for 2 weeks
Nocker 2000	Randomised parallel group study to evaluate the usefulness of induced sputum as an alternative to bronchoalveolar lavage. Excluded as treatment not adjusted according to sputum eosinophils
Prehn 2000	Excluded as randomised to serum eosinophil cationic protein levels. A pilot study of 21 asthmatic children, allocated to receive budesonide 200ug twice daily if ECP between 15-30ug/l or budesonide 400ug twice daily if ECP >30ug/l
Smith 2005	Randomised, single blind, placebo controlled trial adjusting corticosteroids based on exhaled nitric oxide versus conventional guidelines. Excluded as treatment not based on sputum eosinophil count

(*Continued*)

Van Rensen 1999	Excluded as treatment not based on sputum eosinophil count. Randomised, double blind, placebo controlled parallel study to compare the changes in non-invasive markers (airway hyperresponsiveness, sputum eosinophils and exhaled nitric oxide) after treatment with inhaled glucocorticosteroids
Wark 2003	Non randomised nor treatment adjusted based on sputum eosinophil count. Review article looking at the techniques of sputum induction, exhaled gas measurements and blood or serum measures as noninvasive measures of eosinophilic inflammation
Wilson 2000	Non RCT. Cross sectional study of children to determine the feasibility of sputum induction, repeatability of sputum eosinophil counts and the correlation to asthma symptoms
Zacharaisiewicz 2005	Non RCT. Prospective, observational study in children using non-invasive measures (exhaled nitric oxide, induced sputum and exhaled breath condensate) to monitor airway inflammation to result in optimal treatment
Zubovic 2003	RCT using serum eosinophil cationic protein (ECP). Excluded as not using sputum eosinophil. One group was treated with disodium cromoglycate and the other corticosteroid flunisolide to see the success of anti-inflammatory treatment by measuring the level of ECP and FEV1

DATA AND ANALYSES

Comparison 1. Any exacerbations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of subjects who had one or more exacerbations over the study period	3	215	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.20, 0.64]
2 Occurance of any exacerbation	3	215	Rate Ratio (Fixed, 95% CI)	0.54 [0.37, 0.78]

Comparison 2. Exacerbations subgrouped by severity of exacerbation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospitalisations	3	215	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.25]
2 Severe exacerbations requiring rescue oral corticosteroids	2	164	Rate Ratio (Fixed, 95% CI)	0.33 [0.19, 0.57]
3 Mild exacerbations	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
3.1 Mild exacerbations over study period	1	96	Rate Ratio (Fixed, 95% CI)	0.83 [0.67, 1.03]
3.2 Severe exacerbations over study period	1	96	Rate Ratio (Fixed, 95% CI)	0.33 [0.16, 0.70]

Comparison 3. Eosinophilic Exacerbations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eosinophilic v Noneosinophilic exacerbations	1		Relative risk (Fixed, 95% CI)	Subtotals only
1.1 Eosinophilic Exacerbations	1		Relative risk (Fixed, 95% CI)	0.28 [0.10, 0.76]
1.2 Noneosinophilic exacerbations	1		Relative risk (Fixed, 95% CI)	1.07 [0.62, 1.85]

Comparison 4. Exacerbations subgrouped by asthma severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mild v Severe asthma	1		Relative risk (Fixed, 95% CI)	0.74 [0.48, 1.16]
1.1 Very mild to mild asthma	1		Relative risk (Fixed, 95% CI)	1.34 [0.52, 3.43]
1.2 Moderate to severe asthma	1		Relative risk (Fixed, 95% CI)	0.63 [0.38, 1.04]
2 Use of LABA	1		Relative risk (Fixed, 95% CI)	0.85 [0.55, 1.30]
2.1 LABA	1		Relative risk (Fixed, 95% CI)	0.53 [0.25, 1.14]
2.2 Not on LABA	1		Relative risk (Fixed, 95% CI)	1.05 [0.62, 1.78]

Comparison 5. Dose of corticosteroids used

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean dose of inhaled corticosteroids per person per day	3	221	Mean Difference (IV, Fixed, 95% CI)	78.99 [-90.13, 248.11]
2 Mean daily use of oral corticosteroids per person per day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 6. Cost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Yearly cost per person (US$)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

WHAT'S NEW

Last assessed as up-to-date: 10 December 2008.

Date	Event	Description
11 May 2009	Amended	Corrected data

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 2, 2007

Date	Event	Description
12 December 2008	New search has been performed	2008 Searches and edited
1 September 2008	Amended	Converted to new review format.
21 November 2007	New search has been performed	New studies sought but none found
2 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Protocol: Written by HP and AC, reviewed by AL, AK, CT

Review: All participated in selection of studies. HP and AC extracted data, performed analysis and wrote review. AL, AK, CT reviewed manuscript. TL and CC assisted with analysis.

DECLARATIONS OF INTEREST

Nil

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INDEX TERMS

Medical Subject Headings (MeSH)

*Eosinophils; Adrenal Cortex Hormones [therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy; pathology]; Leukocyte Count; Randomized Controlled Trials as Topic; Sputum [*cytology]

MeSH check words

Adult; Child; Humans